119. The array as recited in claim 117 comprising more than 1000 groups of oligonucleotides of known sequences.

120. The array as recited in claim 117 made by the process of:

exposing a first region of said substrate to light to remove photoremovable groups from nucleic acids in said first region, and not exposing a second region of said surface to light;

covalently coupling a first nucleotide to said nucleic acids on said part of said substrate exposed to light, said first nucleotide covalently coupled to said photoremovable group;

exposing a part of said first region of said substrate to light, and not exposing another part of said first region of said substrate to light to remove said photoremovable groups;

covalently coupling a second nucleotide to said part of said first region exposed to light; and

repeating said steps of exposing said substrate to light and covalently coupling nucleotides until said more than 500 nucleotides are formed on said surface.

Please add new claim 121 as follows:

--121. The array as recited in claim 117 comprising more than 10,000 groups of oligonucleotides of known sequences.--

REMARKS

I. General

Claims 105, 107-115, and 117-120 are pending. By way of this amendment, claims 110-114 and 117 are amended. Claims 105 and 107-109 are cancelled.

II. Rejections Under 35 USC 112, First Paragraph

A. Density

The specification has been objected to under 35 USC 112, first paragraph and the claims are rejected as not being enabled, and the claims have been similarly rejected. The Examiner points to the article in Science wherein an experiment with 65,000 sites is discussed in one paragraph written by Marcia Barinaga. Reconsideration of the rejection and allowance of the claims are respectfully requested.

First, Applicants point out that it is the Examiner's burden to demonstrate non-enablement (_). The Barinaga article (a one page, third party, article about the present technology and several others) does not in any way demonstrate non-enablement of the claimed subject matter for many reasons, some of which are listed below:

a) The article does not on its face say anything remotely implying that larger numbers of synthesis sites are not enabled. The Barnaga article mentions in passing an experiment performed by/for one of the inventors herein wherein 65,000 sites are placed in a 1.28 cm square array. Applicants cannot see how this might imply that higher numbers of sites are not feasible.

b) The Examiner must make a number of logical leaps that are simply not reasonable based on the Barinaga article. For example, the Examiner must presume that the (third party) author has reported, in a single paragraph, the situation correctly and fully as it was discussed with Dr. Fodor. Further, the Examiner must presume that this **single paragraph discussion** fully reports all of the capabilities of the scientists quoted therein. In a normal commercial context, a scientist is for obvious reasons wary of fully disclosing every capability of its company to an outside reporter during the early stages of the company's development.

c) In fact, an earlier paper by scientests involved with this technology demonstrated that higher resolution was already achieved. The earlier Science paper by these scientests (copy enclosed) revealed that resolution of 25 um was achieved. See page __. In only a 2x2 cm area, this would provide 1 million synthesis sites.

Still further, even if the article did in some way imply that 65k chips were the limit of the technology disclosed in the specification of this application, this does justify a rejection of the subject matter herein. The claims herein recite, for

example, more than 500 synthesis sites. 35 USC 112, first paragraph, requires only that the application be enabling for a reasonable number of embodiments within the claim scope (_). Even if the application were enabling for only 65k chips, it is clear that the claims are enabled over 3 **full orders of magnitude** of density. Clearly, the requirements of 35 USC 112, first paragraph are met by the present application for at least the independent claims.

Even further, the Examiner fails to consider the pioneering nature of the present invention. As the Examiner is no doubt aware, the present invention was placed second in the inventor of the year competition. The original Science article won the American Association for the Advancement of Science Newcomb Cleveland Prize as a paper that included "original research data, theories, or syntheses [that are] fundamental contributions to basic knowledge or technical achievement of far-reaching consequence." These are only two of the honors that have been bestowed on the present technology. Given that pioneering inventions are entitled to a broader range of enablement than other inventions, the present claims are clearly enabled.

However, perhaps most important of all, the assertion that the present application is not enabled for high density arrays is simply not correct. The technology disclosed in this application has, in fact, been used to synthesize high density arrays. A declaration of one of the inventors herein (Dr. Fodor) is enclosed herewith. The declaration discusses an experiment wherein the technology disclosed in the present application was used to form an array of more than 1,000,000 oligonucleotide molecules at known locations on a substrate. Clearly, the present claims are enabled under 35 USC 112, first paragraph.

B. Covalent Attachment

The Examiner asserts that claims 105 et seq. are enabling for only covalently attached oligonucleotides. Applicants do not agree with the rejection and intend to pursue claims of a broader scope in a continuation or other related application. However, the claims remaining herein are limited to covalently coupled oligonucleotides.

III. **Rejections Under 35 USC 112, Second Paragraph**

Claims 105, 110, and 117 are rejected as indefinite. The Examiner objects to the term "predefined." Although it is believed that one of skill in the art would understand that which is claimed, the claims have been amended to consistently refer to simply "known" locations. Clearly, one characteristic of the substrates herein is found in the knowledge of which sequence(s) are at which locations of the substrate. Accordingly, it is believed that the rejection is overcome.

Claim 105 is rejected as unclear as not sufficiently relating the oligonucleotide molecules to the predefined regions. The claim has been cancelled without prejudice, rendering the rejection moot. Accordingly, it is believed that the rejection is overcome.

IV. **Rejections Under 35 USC 102(e)**

Claim 105 is rejected under 35 USC 102(e) as lacking novelty over Drmanac et al. The claim has been cancelled without prejudice, rendering the rejection moot.

V. **Rejections Under 35 USC 103**

A. Khrapko et al.

Claims 105, 107-115, and 117-120 are rejected under 35 USC 103 as unpatentable over Khrapko et al.

Claim 105 has been cancelled, rendering the rejection moot in the present application. Claim 110 has been amended to recite that the various oligonucleotide molecules occupy a total area of less than about 1 cm^2. By contrast, Khrapko et al., which proposes without any enabling disclosure, that 64,000 oligonucleotides be placed on a solid support in regions of 2 mm dots. At this scale, 1000 oligonucleotide probe regions would occupy 40 cm^2. Accordingly, it is seen that the material in claim 110 provides for the placement of 1000 oligonucleotide probe regions in an area that is a full one and one half **orders of magnitude** smaller than the region proposed by Khrapko et al., **even if Khrapko et al. was somehow able to place the probes on the support without any "space" between the probes.** Although

applicants do not in any way concede that Khrapko et al. would be enabling at this scale, the point is rendered moot by the present claims.

For a reference to render a claim obvious, the reference must have some affirmative suggestion to the claimed combination. Clearly, Khrapko et al. do not show or in any way suggest the densities recited herein. The paper cited by the Examiner is actually put forth as showing various "refinements" to the method, along with experimental data. Even this "refined" statement of the Khrapko et al. technology provides only 2 mm dots for the placement of probes. Further, in the experimental discussion, Khrapko et al. shows only three such probes, and even here it is not clear that they are on the same substrate. Based on the "refined" teachings of Khrapko one of skill in the art would clearly be led to the 2 mm dot blot technology for placement of probes on a substrate. There is simply no showing or suggestion in the reference that higher densities are possible, or enabling teaching as to how one would form high density arrays such as those claimed herein. Accordingly, the rejection should be withdrawn.

B. Southern et al. in view of Lowe et al., Clark et al., or Schnur et al.

Claims 105, 107-115, and 117-120 are rejected under 35 USC 103 as unpatentable over Southern et al. in view of Lowe et al., Clark et al., or Schnur et al.

As an initial matter, the subject matter of at least one of the references cited against the present application is not prior art to the presently claimed invention. Southern et al. (WO 89/10977) was published on November 16, 1989. This is a full 5 months after the filing date of the parent application to the present application. Note, e.g., claims 45 and 48 of the parent application filed June 7, 1989. Accordingly, the Southern et al. reference is not prior art under section 103 of the patent statute.

However, even if the Southern et al. reference were prior art to the present application, Applicants assert that Southern et al., alone or in combination with the other references, does not in any way render obvious the presently claimed invention. As the Examiner notes, the Southern et al. reference speculates as to several methods of forming substrates including the use of a pen plotter, printing

device, or by masking with silicone rubber. The ENTIRE disclosure of Southern et al. relating to the synthesis technique is found at pages 11 and 12. According to the explicit teachings of this brief discussion Southern et al. candidly admits, in a statement that is rare among the teachings of a patent application:

> **AUTOMATIC EQUIPMENT FOR APPLYING THE PRECURSORS HAS YET TO BE DEVELOPED.** (Southern et al., page 11, emphasis added)

Southern et al. continues to candidly admit throughout the discussion at pages 11 and 12 that all of the possible techniques proposed therein are merely "possibilities." Under the circumstances, it seems beyond pale that the Southern et al. teachings could not possibly be considered enabling for the claimed subject matter herein where more than 1000 oligonucleotide probes are placed within a region of less than 1 cm^2.

The Examiner points particularly to the reference to 100 micron sites on a paper support which Southern proposes as a "fairly comfortable upper limit." Initially, this statement must be taken in context of the two pages of disclosure regarding substrate fabrication. Quite clearly, Southern et al. proposes this limit as some sort of theoretical limit **once the enabling technology is developed.** Southern et al. do not, even themselves, believe that this technology is enabling for the invention claimed herein.

Even though it is the Examiner's burden to show that the prior art is enabling, even the other Southern references cited by the Examiner provide extrinsic evidence that the Southern application is not enabling of the material claimed herein. Note page 1010 of the Southern et al. Genomics paper. At page 1009 of the Southern et al. paper, Southern states that 1000 oligonucleotides have, several years later, been placed on a substrate in an area of 96 mm by 96 mm, i.e., an area that is still, years later, two full orders of magnitude larger than the substrate recited herein. Accordingly, it is seen that the frank statements about the limitations of the Southern et al. arrays in the cited application hold true, even years later Southern tries without success to make arrays of the densities recited herein.

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Lowe et al. is tentatively combined with Southern et al. to reach the claimed subject matter herein. However, even to the extent that Southern et al. is prior art, and even to the extent that it could be considered enabling, Lowe et al. teaches directly **away from** the invention claimed herein. As recited herein, the present invention provides for the fabrication of many sites wherein **different** oligonucleotides are formed. Lowe et al. suggests the formation of a biochemical MOSFET, a commonplace device in the semiconductor industry. However, when those of skill in the art fabricate semiconductor devices such as those of Lowe et al., thousands or millions of the **same thing** are fabricated on a single substrate. Diversity is abhorred. Hence, the teachings of Lowe et al. would lead one directly away from combination with the admittedly non-enabling teachings of Southern et al. Conversely, the teachings of Southern et al., where those of skill in the art are struggling to **create diversity** would in no way be combined with those of Lowe et al., and in fact one of skill in the art would be led directly away from the combination. Accordingly, the combination would not have rendered the invention obvious since it is not in any way shown or suggested in the references.

The Examiner alternatively combines the non-enabling teachings of Southern et al. with Clark et al. Clark et al. appears to be somewhat less relevant than even Lowe et al. The technology of Clark et al. is directed to the fabrication of "nanostructures." As noted at column 1, line 13 Clark et al. suggests that "nanostructures" are electronic, optical and/or bimolecular devices of nanometer size. Accordingly, it is seen that Clark et al. are directed to similar technology as that of Lowe et al. The attempt of Clark et al. is to form many of, again, the same thing but at a smaller size than Lowe et al. See column 10, line 41 et seq. A "screen" is formed to produce these devices. See column 14, line 7 et seq. In this section of the disclosure, Clark et al. are attempting to form a "nanometer size memory." As with Lowe et al., Clark et al. would form an "array" of **exactly the same type of memory "cell"** or the memory would, line a semiconductor memory, be of no use. Accordingly, the combination of Southern et al. with Clark et al. also falls short of the claimed invention.

In another alternative combination the Examiner applies Schnur et al. with the non-enabling disclosure of Southern et al. Again, Schnur et al. relates to a technique for forming integrated circuits. The technique differs from conventional semiconductor techniques in that "differing areas of reactivity" are formed on a substrate and, thereafter, metal or other material can be coupled to the substrate. The Examiner points to column 8, lines 27-41, to show suggestion to use the technique for polymers. However, this is not related to the "polymers" taught herein. The polymers suggested by Schnur et al. are used as the resist-like material on the substrate. Schnur et al. in no way shows or suggests that the technique therein be used to form an array of polymers; quite the reverse, Schnur et al. are teaching that polymers should be used in the fabrication of semiconductor devices and, in particular, metal regions on a semiconductor device. And, again, Schnur et al. is trying to form semiconductor devices. Formation of **different** materials would in no way be shown or suggested. Accordingly, the rejection should be withdrawn.

SUMMARY

For the reasons cited above, reconsideration of the rejection and allowance of the claims are respectfully requested. If the Examiner believes that a telephone conference would in any way facilitate review of the application, the Examiner is invited to contact the undersigned attorney by telephone at (415) 326-2400.

Respectfully submitted,
TOWNSEND and TOWNSEND KHOURIE and CREW

Date: _____

By: _____
Vern Norviel
Reg. No. 32,483

Enclosures:
Declaration of Stephen P.A. Fodor
Science, Fodor et al.